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Editor
ROY WALDO MINER

Contents

A New Personality Test: The Graphomotor Projection Technique. *By* SAMUEL B. KUTASH 44
The Tomkins-Horn Picture-Arrangement Test. *By* SILVAN S. TOMKINS 46
North Atlantic Deep-Sea Sediments and Submarine Canyons. *By* DAVID B. ERICSON .. 50
Symposium on Carbonic Anhydrase Inhibition as a Physiological Tool:
Pharmacological and Renal Effects of Diamox (6063), a New Carbonic Anhydrase Inhibitor. *By* THOMAS H. MAREN 53
Carbonic Anhydrase Inhibition and Gastric Secretion. *By* HENRY D. JANOWITZ, HENRY COLCHER, AND FRANKLIN HOLLANDER 54
The Role of Carbonic Anhydrase in Pancreatic Secretion. *By* FRANKLIN HOLLANDER AND DAVID BIRNBAUM 56
Studies on the Structure of Pyrimidine Glucoside Vicine. *By* AARON BENDICH 58
Conference Held 60
New Members 61

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Executive Director: EUNICE THOMAS MINER

A NEW PERSONALITY TEST: THE GRAPHOMOTOR PROJECTION TECHNIQUE*

By SAMUEL B. KUTASH†

A technique has been developed that is simple to administer, not too time consuming, yields dynamic material capable of direct application in clinical psychodiagnosis and therapy, and lends itself readily to use in busy clinics and hospitals, where time is at a premium. In spite of its brevity, the method is comprehensive, including both verbal and nonverbal performance and involving, successively, graphomotor expression, recall, ideation, kinesthetic perception, visual perception and projection, and content and verbal association. A graphomotor record is obtained with visual perception excluded by blindfolding. This is followed, in turn, by a study of the subject's immediate recall of his performance and his ideation. Then, with the removal of the blindfold, visual perception is introduced, and various aspects of the personality are studied as they reveal themselves in the subject's projections and delineations of content. The last phase of the test involves study of the subject's associations to the content.

The test can be administered either by the clinical psychologist as part of a psychodiagnostic battery (in which case it adds information not as readily revealed by other techniques) or by the trained psychiatrist or psychologist during the course of treatment, in order to evaluate personality changes or to secure a graphic record of progress in therapy. The patient's characteristic defenses and resistances as well as his probable response to therapy are revealed.

The nature of the directions permits the subject wide latitude in expressing himself in graphomotor fashion, providing a suitable outlet through which his total personality, including emotions, thoughts, and reactions are projected. The blindfold excludes visual impressions and their accompanying distractions and, thus, facilitates the emergence of inner promptings uncontaminated by perceptual responses to external visual stimuli. The amorphous nature of the graphomotor production required, in contrast to more structured graphic forms of expression, such as figure drawing, copying of designs, and handwriting, leaves less room for conscious censorship and the application of previous learning patterns.

*Description of the Method.** The subject is seated comfortably before a table and given a pencil and two sheets of paper (9 x 9 in.). He is then blindfolded and told to move the pencil freely on the paper but try not to plan to produce anything definite. He is to let his hand and mind go freely. The subject has five minutes to work on the first sheet and five minutes on the second. If he makes or writes any numbers, letters, geometrical figures, pictures, words, or form designs on Sheet 1, he is instructed, when Sheet 2 is presented, not to make or write any numbers, pictures, *etc.*, depending upon which of these structured items he produced previously. Before the blindfold is removed, the subject is requested to tell what he made on each paper and what his thoughts were during the test. The blindfold is then removed, a sheer onionskin paper is placed over the protocol, and the subject is asked to identify and trace any structures or content in the productions that he can see or imagine. He then associates freely to the content identified.

The examiner records† initial reaction time, spontaneous comments made by the patient, the examiner's own qualitative observations on the subject's performance, the subject's verbatim recall of the nature of the production, his verbalized ideation during the performance, the number and kinds of pauses and breaks, the amount of pressure on the pencil, the speed and the quality of the movement, the types of markings, the number of times the pencil goes off the page, the content identified, content-identification time, and certain other items.

* This paper, illustrated with lantern slides, was presented at the meeting of the Section on October 20, 1952.

The graphomotor projection technique was developed jointly by Raymond H. Gehl, M.D., and the author. The clinical and statistical research was aided generously by support from the Veterans Administration. The normal cases were collected largely through the cooperation of Dr. Hadley Cantril and the staff of the Office of Public Opinion Research, Woodrow Wilson School, Princeton University. The schizophrenic patients were examined mainly at the Newark VA Mental Hygiene Clinic and the Lyons VA Hospital. The complete manual for the technique and report on its clinical use and standardization is in press.[2]

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* The detailed, precise directions are available in a mimeographed manual[1] and will appear in a forthcoming monograph.[2]

† Blanks and materials for recording and scoring are also available and can be obtained from the authors.

TABLE 1
SUMMARY OF SIGNIFICANT DIFFERENCES

Normals	*Schizophrenics*
Unstructured records	Structured records
UCR, UCF, UVP, SO, and UM (2)	UB, UL, US, O, SN, SW (1) UB, UL, O, SN, UCD, UH (2)
Moderate density	Very low density, W, P, O (1)
Very high density (1)	P, O (2)
57 to 64 boxes of space filled	8 or less boxes of space filled or no production
Moderate pencil pressure	Heavy or very light pencil pressure (1)—light (2)
Moderate and light in combination Heavy and moderate in combination (2)	
Circular and wavy movements	Linear movements
Various other types of markings in combination including all 5 types of markings	Writing of words or sentences No markings at all (1) Lines and zigzags (2)
Smooth movement	Spasmodic movement
Fast and moderate, moderate and slow, or just moderate speed of movement	Very slow (2)
No pauses	1–10 pauses (1)
No breaks (1)	Over 20 breaks
1–10 breaks (2)	
Stay on page (1)	More often go off the page (1)
Start instantly or in 1 to 4 seconds	Delayed reaction time
Recall nature of production accurately	Bizarre descriptions, failure to recall, lack of awareness of nature of production
Follow directions	Do not follow directions
Ideation concerns interpretation, personal fantasies, performance itself, external stimuli, alone or in combination	Bizarre fantasies or bizarre responses, blocking

The protocol is scored for gross structuring, classification of the total configuration, graphomotor type, and amount of space filled, using specially devised scoring schemata. An evaluation is made of how well the subject followed directions, the accuracy of his recall of the nature of the production, and his ideation during the performance. Some of the quantitative scoring is performed with the aid of a celluloid scorer divided into 64 boxes, which is placed over the protocol.[4]

The major types of protocols are encompassed by a classificatory system based upon the major attributes and predominant features of the records. These types are as follows:

UB	Unstructured, Broken
UCD	Unstructured, Continuous Dysrhythmic
UCF	Unstructured, Continuous, Finger Movement
UCR	Unstructured, Continuous, Rhythmic
UE	Unstructured, Empty (Low Productivity)
UH	Unstructured, Hieroglyphic
UL	Unstructured, Linear
ULI	Unstructured, Linear, Intersecting
UM	Unstructured, Mixed
US	Unstructured, Spiral
UT	Unstructured, Twining
UVP	Unstructured, Variable Patterning
O	No Production
SA	Structured, Alphabet
SE	Structured, Exercises
SM	Structured, Mixed
SN	Structured, Noncoordinated
SO	Structured, Organized
SP	Structured, Patterning
SW	Structured, Writing

The ideation during the performance is scored in accordance with whether it referred to or contained fantasies unrelated to the performance, feeling about the test, thoughts concerning how the material is to be interpreted, the performance itself, references to external stimuli, and/or bizarre responses.

Comparative Study of Normals and Schizophrenics. Four hundred subjects were used in a validation study, divided equally into two groups: an *experimental* group consisting of 200 well-substantiated schizophrenic patients, and a *control* group composed of 200 apparently normal persons. The experimental design of this study and the statistical findings are reported fully elsewhere.[1] The significant differences found are summarized in TABLE 1.

Interpretive Principles. For the past five years, the graphomotor projection technique has been used extensively by the authors and others with a variety of subjects (over 2000) covering the entire gamut of diagnoses, including minor personality maladjustments; anxiety, obsessive-compulsive, and other types of neuroses; mild and severe psychoses; organic conditions of various kinds; and psychosomatic illnesses. Interpretive principles have been elaborated based both upon the findings of our comparative study of schizophrenics and

normals and upon extensive clinical experience with the technique.

The key to the understanding of the graphomotor production lies in the consideration of the nature of the task set for the subject. This task is essentially a suggestion to produce free psychomotor activity without structuring the performance. The majority of normal individuals will respond to this suggestion by an unstructured, rhythmic, continuous record covering a large portion of the page with more or less even, medium pencil pressure and moderate speed. The protocol consists usually of circular and wavy movements including occasionally linear motion. There are few breaks and pauses and infrequent goings off the page. The material is distributed evenly throughout the paper. The content produced is distributed evenly throughout the paper. The conflict produced in the normal individual by offering the suggestion is minimal. The "meaningless" nature of the production facilitates his expression, and the lack of tension allows for less utilization of defense mechanisms. The performance is thus relatively free of inhibition, interruption, and dysrhythmia.

Other individuals will respond to the test situation in a variety of ways that will reveal their anxiety, pathological trends, and/or defense mechanisms. In the neurotic individual the directions set up a conflict situation. He does not feel able to respond with freedom of movement in what seems to him a meaningless, unstructured way. He has a need to either structure the performance, thus binding down the anxiety, or to express the anxiety, through inhibited movements, heavy pencil pressure, tremulousness, coarctation, and other deviations from the normal unstructured performance described above. The psychotic patient usually either fails to respond to the directions, projecting his inner life in the form of noncoordinated, structured material, or he produces an unstructured performance that is linear, dysrhythmic, or broken and discontinuous.

For the interpretation of specific psychomotor patterns and of individual cases, the reader is referred to our previous publications.[2, 3] It has been found that a dynamic picture of the total personality can be secured by the interpretive integration of the indications secured from the various aspects of the performance both scorable and qualitative.

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THE TOMKINS-HORN PICTURE-ARRANGEMENT TEST*

By SILVAN S. TOMKINS†

The Logic of Test Construction

The author of a psychological test first conceives of a method that will elicit information from and about human beings. His method may yield more or less information than do other methods, or the information obtained may be of a different nature. Test methods typically, yield less information than long-term observation or free-association interviews produce. The sheer quantity of data is a matter of indifference, however. The information must permit inferences beyond itself. A crucial experiment may call for the complete reorganization of the foundations of a science. If a test is, in the first instance, a method of gathering information, so is observation, so is free association, and so is experimentation. What, if anything, distinguishes the test method from other methods? An experiment is the occasion for testing new ideas growing out of the fabric of the science. It is repeated, if at all, only to make certain that what seemed to happen once really did happen. After a few replications, there is no point to further repetition of the same experiment. If an experiment raises more questions than it answers, it has not been in vain, since new experiments can and will be designed to answer these questions. This is indeed the essential dynamic in experimental science. Ordinarily, however, a test is designed for repeated use, since it attempts to answer a limited question or set of questions in a very definite way. Thus, a test for pregnancy answers answers the question with a yes or a no. A test for blood pressure tells whether the individual has one of a limited number

* This paper was presented at the meeting of the Section of Psychology on November 17, 1952.
† Department of Psychology, Princeton University, Princeton, New Jersey.

of blood pressures. We should not expect such a method to answer all the questions we might conceivably ask about a human being or to be a continual source of fruitful hypotheses about the nature of personality. Specialization of method is clearly profitable, but there is a price we must be prepared to pay. If the test method is to yield us information from which we can draw limited, precise, and true inferences mechanically and with little pain and great regularity, then we must forego the power of the experimental method, the suggestiveness of the method of free association, or such procedures as the Thematic Apperception Test. The latter is a method comparable, in the wealth of material it elicits, to the free association method. The information obtained by it may be used for many purposes. It is specialized for none of its present uses, and I doubt that it will ever be "standardized," any more than the experimental method will be standardized. It will continue to be useful in the generation and testing of hypotheses, but it will be a *test* of nothing in particular.

The clinician today is loath to give up information. He is acquisitive and retentive about every last scrap of information that present clinical procedures afford him. If he can not immediately use all the information he collects, he is unwilling to relinquish it, lest he need it at some future date or because it might have some unsuspected significance in the light of still more data collected in the course of further interviews. Praiseworthy as this attitude may be, it has been an obstacle in the construction and acceptance of tests of limited scope. The clinician is apt to favor a method that promises everything over a test that answers specific questions with certainty. In part, he is objecting against being reduced to a technician. This is as it should be, but testing in the strict sense of the word should not demand more than the competence of a technician.

If one accepts this view of the limited objective of the test, one is faced with a peculiarly difficult problem. It derives from the most characteristic and significant ability of the human being: the ability to solve a problem and to achieve the same end in a variety of different ways and for a variety of different purposes. If, in test interpretation, we must be able to infer some inner state or characteristic of the respondent from a particular response, then his competence stands squarely in the path of our solution of the problem. The same response can be made for a variety of reasons by individuals who differ in almost every way, except that they gave the response. If I ask a person his name, the correct answer may be given by a bright or a dull person, by a friendly or a hostile individual, by a Protestant or a Catholic. We can, indeed, infer something from this response; *e.g.*, that the respondent has some knowledge of English, that he is not totally deaf, but beyond such generalities we cannot go. The paradox for the tester consists in the fact that the most stable responses are least diagnostic because one can make so many inferences about the person that it becomes equivalent to saying nothing about him. The new information is minimal under such conditions. It is this phenomenon that has complicated the investigation of cortical function in general. Removal of cortical tissue characteristically leaves such overlearned responses unchanged, even though the underlying mechanism was, in all probability, influenced adversely.

The solution offered by the projective tests is essentially based upon a kind of response most unlike the type we have been discussing. Instead of dealing with items and responses that anyone would give, no matter what kind of person, or what kind of mood, they have used a stimulus and a task most calculated to produce variation between individuals and within the performances of a single individual. This has presented another problem. If I cannot infer very much from the fact that you say "good morning" when I say "good morning", I am not very much better off if I ask you simply to tell me the first word that comes to your mind, apropos of nothing at all. We may be sure that that word will differ from the word given by the next respondent, but it will also differ from the word that you will give me tomorrow. To maximize variability of response complicates the validity problem no less seriously than minimizing variability, for, although each word in such an experiment has a "cause," it will not be easy for the tester to infer what this cause might be.

The projective testers have therefore taken a middle position. They use material and tasks that anchor the individual somewhat. Variability, intra and inter individuals is encouraged, but kept within limits. Inference with projective material becomes uncertain when the variability is too reduced or too great. The logic of interpretation rests essentially upon the rare or improbable response. In the Thematic Apperception Test it is

commonly found that each story to each picture is to some extent different from every other story. A complete analysis of the parameters of variation in the TAT stories of a thousand individuals would involve astronomical magnitudes. Since this is the case, the probability of any one response is very small. At this point, we cannot be certain about the personality of the story teller, since he might have given any one of a thousand other stories. It is only when we find that, to several different pictures, he repeats the same improbable response that we are justified in drawing inferences about the structure of the person who insists upon this most improbable occurrence, *i.e.*, the conjoint production of a *series* of the *same* improbabilities. The probability of such a phenomenon is the product of the separate probabilities. It is as though we asked a person his name and he did not answer. We might suppose that the probability of such a phenomenon is very low and that it might safely be ascribed to a limited number of possible causes. Either he did not hear because he was deaf, or we spoke too low; or he heard but did not understand because he did not know English, or he was extremely unintelligent, or aphasic, or extremely frightened. If now we walk behind him, clap our hands, and elicit no startle response, the possibilities are even more drastically reduced, because the conjoint phenomenon of no name and no startle is even rarer, and the probability that the individual is deaf is very high, though not certain. Only a diagnostician who knew how rare the inability to respond with one's name and the lack of startle were could infer deafness on this basis, however. So too in the utilization of projective material, we necessarily depend upon the experience and special sensitivities of the interpreter to sense the idiosyncratic. It is an art that can be taught and cultivated, but the possibilities of error are always great.

The Tomkins-Horn Picture-Arrangement Test

Our solution to this problem is a simple one. Instead of using relatively unstructured material and relying upon the sensitivities of the interpreter, we employ highly structured material that yields relatively low inter-individual variability, discard most of the responses, and utilize for diagnostic purposes *only* the rare responses. It is as though we asked each person his name and waited until we found an individual who said he did not know his name. We would be prepared to say something definite about this person. But what we have gained in certainty we have lost in efficiency. We might test a million people with this method before we found one about whom we were willing to make a diagnosis. This is, I think, a necessary consequence of our method. In the PAT, the individual responds in one of six ways to each of twenty-five plates. Since each plate has but one or two common responses, it might happen that a particular individual gave no diagnostically significant responses, since these are statistically rare. Our only opportunity for eliciting rare responses to highly structured material can only consist in radically increasing the number of responses. This, however, is impractical for the psychotic population, and too costly of time and energy for the remainder of the population. My solution of this efficiency problem consists in combining *groups* of responses, and considering the probabilities of series of responses. Thus, one may ask with regard to five particular plates how common it is for an individual to give the five common responses *conjointly*. It will be found that there are now a few more rare responses, since it may be statistically rare that an individual selects every one of the modal responses in these particular plates. By combining and recombining sequences of responses, we are enabled to increase the total number of responses and, hence, the number of rare responses, without unduly taxing the subject.

The PAT was originally designed for purposes of selection and guidance of industrial personnel. When it proved effective, it was revised for more general purposes. It is approximately ten years old, and we regard it as still in the experimental state. It is available to individual psychologists but has not yet been released for general use. It was designed for group testing and for machine scoring. The advantages of both of these features in a projective technique needs no underlining. The present-day expenditure of time and energy in administration and scoring of our standard projective procedures effectively renders large scale testing unfeasible.

The test consists of twenty-five plates, each containing line drawings of three different but related situations, with the same "hero" depicted in all plates. It is the subject's task to say or write in what order these three situations should be placed to make the most reasonable sequence. He is asked to indicate this order by means of three symbols (a triangle, a rectangle, and a circle) that

appear in each plate at the bottom of each line drawing and which are to be reproduced in the appropriate order on three successive lines at the bottom of each page. The three drawings are shown at angles of 120 degrees apart, so that one drawing is always upside down. The plate must therefore be rotated to be completely inspected, and no particular sequence of drawings is favored. It is hoped that position factors have been randomized in this way. There is upon the page opposite the instruction page an illustrative plate, which is so drawn that there is but one interpretation that is reasonable and which is reproduced as a sample response. This is done in order to reduce the probability that the subject will appreciate that there might be more than one plausible interpretation for each plate. This seems, in general, to have been a successful device. The average subject is quite surprised when he discovers that there are occasionally equally plausible, alternative interpretations. The subject is also required to write a sentence on each of the three bottom lines of each page explaining briefly what is going on in each situation. This was required originally to test the hypothesis that, without benefit of the written response, the sequence chosen was sufficient for scoring the test. Examination of the short stories told by different subjects who selected the *same* sequence of situations disclosed that the original assumption was unsound. Several subjects who agreed upon the same sequence in plate one (first, the hero is shown working at his machine; second, the hero is shown working at his machine, but daydreaming of resting elsewhere; and third, the hero is shown standing beside his machine) varied as follows in their written interpretation of this sequence: "The man is working, but dislikes it and begins to daydream and finally quits," and, "This man is working hard and then he happens to think of his vacation and finally he has finished his day's work." It is clear that machine scoring of these two interpretations as the same response would have done some violence to the facts. Other plates were more successful in that the same sequence produced little variation in interpretation and could presumably have been more appropriately machine scored.

In the original plan for the interpretation of this test, we attempted to make each of the three situations as structured as possible, in order to remove every possible ambiguity, so that the variability of response would be *entirely* a function of the permutations of these elements, in the manner in which a language employs a basic fixed alphabet of limited elements to express a very much larger array of meanings. If we had succeeded in this, then the greatest burden of interpretation, we thought, could have been placed upon the machine. When we discovered that we had failed in reducing the variability of interpretations for the same sequences, we proceeded to complex coding procedures, inasmuch as we were operating upon the prevalent assumption that it is sinful to discard information, that variability must be respected wherever it shows itself. Thus, all the parameters of variation introduced by our subjects had to be catalogued. The scope of this task was such that one of my assistants spent a year coding the different responses to plate one. We were well on our way to having produced a test not unlike the Thematic Apperception Test. It is as though we had decided to use an item like the "good morning" response to the tester's "good morning" only to discover that there were good mornings that were melancholy, good mornings indistinguishable from sneers, and very happy bubbling good mornings. We were misled by the obvious differences in the responses into believing that we had to use these differences and that we could not disregard them. It has only been within the recent past that the solution became apparent, that all of these common responses, plus their minor variations, must be given up. Since this is a most recent insight, we are only now at work rescoring our protocols.

Such qualitative coding as we have done in the past has not been unrewarding, however, although, in the long run, I expect more from the mechanical scoring that we are now undertaking. As an instance of the latter, consider the case of the position in the sequence in which a man shown working is placed. There are fourteen plates in which such a situation occurs. Any subject who in *all* of these widely different plates *always* ends with his hero working, or *never* ends with his hero working may confidently be supposed to have an unusually strong or weak work interest, or to be unusually active or passive. This is empirically a very rare series of interpretations, because in some of the plates the hero is in the hospital, in others he appears very tired, again he seems very angry, and so on. It may be assumed that any person who imagines that another person would always return to work, no matter what the circumstances, is himself strongly work oriented. We have found, in

fact, correlations of this type in connection with scholastic over- and underachievement.

Perhaps the most interesting findings that came out of our qualitative codings of the responses were the schizophrenic reponses. There were two types of situations shown that were systematically misinterpreted by the schizophrenic population. Situations depicting physical aggression or feelings of hostility and situations depicting physical injury, more specifically a man bleeding, were reinterpreted so that the men were not fighting, the hero was not angry, nor was he bleeding. It is of interest that the distortions were not entirely capricious. They are the next best interpretation if one will not give the obvious interpretation of the situation. Thus, the man whose finger is bleeding is sometimes seen as whittling wood, and the blood is interpreted as wood shavings or, sometimes, as semen of a man who is masturbating. Less frequently, the distortion is in the opposite direction, and the hostility and the injury are both very much exaggerated. We believe, on the basis of these findings, that the chronic schizophrenic is in fear of his life, afraid of being killed either by accident or by aggressive assault, and that this is why he needs and accepts a lifetime of institutional confinement. Further, we predicted that manic patients who had had more than one institutionalization differed from chronic schizophrenics in suffering primarily from guilt concerning their own feelings of hostility, and that the episodic nature of this syndrome coincided with peaks of guilt that eventually subsided producing spontaneous improvement and then a recurrence of the disorder when undischarged hostility produced excessive guilt. We predicted, therefore, that the manics would also deny the fact of aggression, as did the schizophrenics, but that they would not deny the fact of physical injury. The results were in the expected direction in that they did deny aggression almost as frequently as did the schizophrenics and in that they did not deny physical injury as frequently as the schizophrenics, although the latter phenomenon was still significantly strong in comparison with normals. It is possible that the criterion of recurrent manic episodes did, in fact, include manics who might later become chronic schizophrenics. Another investigation will have to differentiate further the manic population for a more crucial test of the hypothesis.

SECTION OF GEOLOGY AND MINERALOGY

NORTH ATLANTIC DEEP-SEA SEDIMENTS AND SUBMARINE CANYONS*

By DAVID B. ERICSON†

During the past five years, more than 400 long sediment cores have been taken at abyssal depths in the North Atlantic by Maurice Ewing, Bruce Heezen, and associates on ships of the Woods Hole Oceanographic Institution and those of the United States Hydrographic Office. Among these, a surprisingly large number have been found to contain beds of well-sorted sand.

Two rival hypotheses have been advanced to explain the occurrence of these sands. According to one of these, the sands were deposited during the Pleistocene epoch at a time or times when sea level was about 5000 meters lower. A serious objection to this explanation is that the sands are interbedded with "red" or brown clay of abyssal facies. Another objection is that in several cores sand composes the uppermost layer. Absence of normal deep-sea sediment overlying the sand forces us to the conclusion that the sand was deposited very recently, probably within the time of recorded history. On the other hand, many cores taken a few tens of miles away, from lesser depths and from stations to landward of the sand cores, contain tops composed of about 30 cm. of foraminiferal lutite containing a warm-water fauna resting conformably on from one-half to several meters of brown clay containing Pleistocene foraminifera characteristic of cold water. The fact that this sedimentary section is repeated in core after core without trace of an erosion interval or any evidence of shallow-water deposition amounts to proof, in our opinion, that sea level in the region of the sand cores has not been lower by 5000 meters at any time during the past several tens of thousands of years.

This evidence does not exclude moderate sea-level changes during the glacial stages of the Pleistocene. On the contrary, there is indirect evidence in the cores that sea level during Wisconsin time was sufficiently low to expose the sediments of the continental shelf to the stirring effect

* This paper, illustrated with lantern slides, was presented at the meeting of the Section on November 3, 1952.

† Lamont Geological Observatory, Palisades, New York.

of storm waves, but such a sea-level lowering must not have amounted to more than a few hundred meters at most.

The other hypothesis explains the sands by deposition from turbidity currents. Experiments by Kuenen[1] have shown that artificial turbidity currents are capable of transporting sand and depositing it in graded layers, that is, layers in which there is gradual decrease in particle size from bottom to top.

Sands from cores taken in an area southeast of the Hudson submarine canyon contain Pleistocene and recent foraminifera of species characteristic of the continental shelf and upper part of the continental slope. These species have not been found in the interbedded brown clays, although hundreds of samples have been examined under the microscope.

Although quartz is the dominant mineral in the sands, there is a fairly large fraction containing various felspars, dark minerals, micas, particles of limestone, red and gray shale, and fine-grained sandstone. Sediment samples from the continental shelf off New York have been examined at the Lamont Geological Observatory. It was found that samples from the shoreward part of the shelf contained fairly pure quartz sand with more or less gray clay. On the other hand, samples from near the outer edge of the shelf and from the upper part of the continental slope contained a mineral and rock particle assemblage closely resembling that of the deep-sea sands. The principal difference between the shallow-water sediments and the deep-sea sands was in degree of sorting. The shallow water sediments contained more or less gray clay as well as a rather wide range of particle sizes in the coarse fraction. This similarity of mineral composition, together with the evidence of the foraminifera, have led us to conclude that the sands occurring in the area southeast of the Hudson canyon have been transported from the continental shelf and the upper part of the continental slope. Similar evidence for transportation from a shallow-water environment is found in other occurrences of deep-sea sands. On the southeast slope of the Bermuda platform, for example, graded layers of well-sorted sand occur at depths exceeding 4000 meters, but the composition is quite different. In place of inorganic mineral particles we find here that the sands are composed of the calcareous debris of organisms living at present in shallow water off Bermuda. Particularly significant are abundant particles of calcareous algae, which must have grown within reach of sun light. Similar calcareous sands have been found in cores from deep water off the Bahamas, as well as in cores taken in the Puerto Rico trough at a depth of about eight kilometers. All these sands are well sorted and, in most layers, there is gradation from coarse material at the bottom to fine at the top. Had the organisms whose debris compose these sands lived *in situ* at a time of low sea level, one would expect to find at least some masses of coral and algae. Furthermore, the low-sea-level hypothesis fails to offer any explanation for the particle-size gradation in beds over a meter thick. Instead, all evidence points to a highly selective agent of transportation.

As I have said, the shallow-water sediments of the continental shelf southeast of New York contain an important fraction of gray clay, *i.e.*, finely divided material that should remain in suspension longer and therefore should be transported farther than sand-size material. Many cores from the nearly level bottoms of depressions in the North Atlantic basin contain layers of gray lutite interbedded with normal dark-brown clay. The basal contacts of the gray layers are sharply defined and frequently marked by a film of silt. The upper contacts are without silt and often poorly defined. The interbedded brown clays, as is to be expected of sediment deposited in water more than 5000 meters deep, contain litle calcium carbonate. The gray layers, on the other hand, are anomalous in containing relatively much calcium carbonate. If these gray layers record changes in the Pleistocene climate or changes in the chemistry of ocean water, one would expect them to be continuous over fairly wide areas. Discontinuity of the gray layers is proven by various long cores containing only brown clay, although taken nearby or between stations at which gray layers have been found. When bottom topography is taken into account, it is seen that cores containing only brown clay come from the tops of rises and gentle slopes, while cores with gray layers come from the intervening depressions. This distribution with respect to topography, while fatal to the climatic change theory, is a strong argument for transportation of the gray sediment by turbidity currents. As was to be expected, the gravity-driven turbidity currents have avoided the topographical highs and sought the lows. We conclude from all this that the gray clay of anomalously high carbonate content is the

fine fraction of shelf sediment that has been carried out beyond the zone of sand deposition.

Similar localization of sand deposition with respect to topography is shown by the fact that cores taken from the divides on both sides of the Hudson submarine canyon are always devoid of sand. Quite different are cores taken in the bed of the Hudson canyon. These contain coarse sand and even gravel. This evidence points to the various submarine canyons as being the routes down which shallow-water sediment has been carried into the deep basins.

According to a conservative estimate,[2] the total volume of sand underlying the area to the southeast of the Hudson canyon is in the order of one hundred cubic kilometers. It would seem that the energy represented by the transportation of that much abrasive sediment is at least within the order of magnitude necessary to account for erosion of the Hudson submarine canyon.

In this connection, the nature of the rocks in which the canyon has been cut is, of course, of great importance. So far, only two kinds of wall rock have been sampled. One is an upper Eocene chalk; and the other, a green pyritic clay of Mio-Pliocene age. Both have been compacted to firmness, but neither has been cemented. Absence of even incipient cementation is evident when fine material from these sediments is examined under the microscope. Abundant coccoliths and discoasters, the minute calcareous remains of organisms, can be seen to be quite free of any deposit of secondary calcite. Erosion of soft sediments such as these would require a minimum of energy.

More important than any theoretical consideration is the evidence that some erosion of the wall rocks did take place when the gravel found in two of the Hudson canyon cores was transported through the upper part of the canyon. In these gravels, in addition to pebbles of hard igneous and metamorphic rocks, there are many rounded pebbles of the upper Eocene chalk and green pyritic clay. Furthermore, sand-size particles of these same sediments occur in some of the coarse-sand beds of the area southeast of the canyon.

Another problem of submarine geology upon which the cores have some bearing is the origin of the continental slope. We know through coring that Eocene chalk crops out fairly high up on the continental slope on both sides of the Hudson canyon. Apparently, the present slope is too steep to retain recent or Pleistocene sediment. Other cores below the slope yield similar evidence. These contain clay breccias and mud-flow layering, indicating that large-scale slumping has taken place frequently on the continental slope. Evidently, the present continental slope is not a surface being built out into the Atlantic basin by addition of more and more sediment. When the Eocene chalk was deposited, however, a much less steep surface must have extended some distance basinward from the present slope. I can think of only two ways in which the present steepness of slope can have been developed. One is through erosion by turbidity currents; and the other, by faulting or, what is essentially similar, monoclinal folding. If erosion is the answer, the amount of material removed has been truly enormous. In comparison, erosion of the canyons becomes mere child's play. Even I, a hard-bitten turbidity currentist, am staggered by this job of excavation.

As yet we do not, I think have sufficient information to decide between erosion and faulting. Tentatively, however, I am inclined to favor the faulting–folding hypothesis, partly in order to avoid overworking our turbidity currents, and partly because faulting seems to fit better into the scheme of late Cenozoic history. The Cenozoic, in contrast with most geological periods, was a time of emergent continents. This was particularly true of the latter part of it. To dispose of the water that formerly flooded parts of the continents, there must have been some increase in the capacities of the ocean basins. If the increased capacity came about through downwarping, some accumulation of strain along the continental margins would be expectable, and that might eventually lead to faulting, accompanied by fairly rapid lowering of sea level, not to any enormous extent but just enough to bring about the climatic change that made possible growth of the continental glaciers. Of course, this in itself does not account for the interglacial stages. Here I agree with Flint[3] that climate, having reached a critical state through uplift of the continents or downfaulting of the ocean basins, might be caused to shift back and forth from glacial to interglacial by relatively minor changes in the amount of heat received from the sun.

I am well aware that there is nothing new in any of this theory. In the past few years new evidence has accumulated, however. My object has been merely to indicate the direction in which some of the new evidence seems to point.

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SECTION OF BIOLOGY

PHARMACOLOGICAL AND RENAL EFFECTS OF DIAMOX* (6063), A NEW CARBONIC ANHYDRASE INHIBITOR†

By THOMAS H. MAREN‡

Following the discovery that sulfanilamide was an inhibitor of the enzyme carbonic anhydrase, and that this effect appeared to promote renal excretion of base, new compounds were explored in a search for a more-specific and less-toxic drug. One of these, Diamox, 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide (6063), is the subject of the following report.

Diamox is well absorbed from the gastrointestinal tract of all species studied, including man. It possesses very low systemic toxicity and is excreted largely unchanged by the kidney. Its clearance is approximately two-thirds that of simultaneously determined exogenous creatinine in the dog. Studies with Diamox and carbonic anhydrase both *in vivo* and *in vitro* show that the interaction between inhibitor and enzyme is reversible.

Following a single dose in the dog, rat, and man, there is a copious diuresis of Na^+, K^+, HCO_3^-, and H_2O. This effect in the dog is largely independent of dose in the range 10–1000 mg./kg. After several days of administration, urinary components return to normal. This restoration occurs even in the face of treatment that maintains a high continued concentration of Diamox in the blood, but the metabolic acidosis that may appear by the second day of treatment continues as long as the dosage is maintained. The degree of acidosis depends, in general, on the dose in the range 1–100 mg./kg./day. Dogs have been kept for 5 months on 100 mg./kg./day of Diamox, with blood pH of 7.0–7.2 and plasma bicarbonate of 10–15 milliequivalents/liter.

Further analysis of details of changes in electrolytes following Diamox reveal the following: (1) When the drug is given, and coincident with the diuresis noted above, NH_4^+ and titratable acidity of the urine are sharply reduced or abolished. (2) There is no marked effect on urinary chloride or phosphate. (3) The Na^+ diuresis is generally of shorter duration and magnitude than the K^+ loss. (4) After a single dose, or three doses at eight-hour intervals in one day, cessation of treatment is accompanied, on the following day, by a sharp rise in urinary ammonia, chloride, and titratable acidity. Urinary excretion of bicarbonate, sodium, and potassium are virtually wiped out in the recovery period. Coincidentally, the systemic acidosis rapidly reverts to normal. (5) After five months of daily treatment and maintenance of acidosis, withdrawal of drug is reflected in the urine only by increased acidity and abolition of bicarbonate. Urinary chloride may rise. Within a few days, normal acid–base balance in the blood is restored. If the dog is then challenged with Diamox, response is no different from that of the first day. (6) During the period of daily treatment with 10 mg./kg. (minimal acidosis) and after the initial diuresis, the stable urinary pattern could be altered maximally by a single larger (200 mg./kg.) dose.

These facts fit the theory that Diamox inhibits renal carbonic anhydrase. The initial diuresis is then primarily due to partial failure of acidification and lowered reabsorption of HCO_3^-. Maintenance of balance during sustained treatment is not entirely understood but, in some way, it appears to be due to a new equilibrium between HCO_3^- and enzyme, dependent on a given level of inhibitor. The continued uncompensated acidosis at higher levels of drug may be due to small continued losses of base that do not appear obviously different from control data, or to extrarenal factors that have not yet been explored.

* Reg. U. S. Pat. Off.

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CARBONIC ANHYDRASE INHIBITION AND GASTRIC SECRETION*

By HENRY D. JANOWITZ, HENRY COLCHER, AND FRANKLIN HOLLANDER†

The Composition of Gastric Juice. The juice secreted by the gastric mucous membrane can be considered as a mixture of two components.[1] One is the acid component, identified with the acid secretion of the parietal cell. This is a solution of hydrochloric acid, 165 *mN*, nearly isosmotic with the plasma. The other is the alkaline or non-parietal component, a mixture derived from the other differentiated cellular elements of the gastric glands, and includes desquamated material and interstitial fluid. Its electrolyte composition is variable but, based upon a study of cell-free mucus, ranges of values of the following order have been observed: Na, 140–166 *mN*; K, 3.0–5.2 *mN*; Ca, 5 *mN*; Mg, 3 *mN*; chloride, 113–151 *mN*; buffer capacity, 12–48 *mN*. This component also contains the mucopolysaccharides and proenzymes.

Although this analysis has enabled us to account for variations in the electrolyte composition of mixed gastric juice, we have had very little insight into the intracellular processes involved in the formation of the components of gastric juice.

The discovery by Davenport and Fisher[2] in 1938 that the stomach contains the enzyme carbonic anhydrase and, especially, Davenport's demonstration[3] that there are large amounts within the parietal cell and some in the surface epithelial cell raised the possibility that this enzyme might be concerned in the secretion of both components.

Carbonic Anhydrase and Acid Secretion. Attempts to inhibit gastric acid secretion by inhibiting the carbonic anhydrase of the stomach in living animals have, until recently, been unsuccessful. Feldberg *et al.*[4] used sulfanilamide, a known carbonic anhydrase inhibitor, in cats; Davenport[5] used sulfanilamide and thiophene-2-sulfonamide in dogs and cats; and Anderson and Wilbur[6] used sulfanilamide in turtles.

With isolated frog and toad gastric mucosae, however, Davies and Edelman[7] inhibited acid secretion *in vitro* with prontosil soluble, *p*-sulfonamidobenzoic acid and *p*-toluenesulfonamide. These investigators concluded that, in previous work, the enzyme had not been sufficiently inhibited to suppress acid formation *in vivo*, since the degree of carbonic anhydrase inhibition required must necessarily lead to the speedy death of the animal by interfering with carbon dioxide transport in the red cell.

The Present Studies. The recent synthesis by Roblin and his co-workers[8] of a new group of heterocyclic sulfonamides with marked carbonic anhydrase-inhibitory power prompted us to reinvestigate this problem.[9] Dogs with vagally denervated (Heidenhain) pouches were used for these experiments, and acid secretion was stimulated by the subcutaneous injections of histamine. When 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide (Diamox, 6063) was injected intravenously into these animals in doses of 20–60 mg./kg. body weight, between 80 and 97 per cent inhibition of HCl output (M = 89 per cent) occurred after a latent period of 20–80 minutes. The inhibition persisted for 3–6 hours, but apparently had recovered by 24 hours. It is interesting that (a) the inhibition manifested by decreased volume flow and acid concentration was never complete; (b) the latent period was related inversely to the rate of secretion at the time of inhibition, and (c) this degree of gastric carbonic anhydrase inhibition was well tolerated. Experiments with 2-benzothiadiazole-sulfonamide in the dose range 20–30 mg./kg. body weight resulted generally in similar inhibition.

Topical Application of Inhibitors. Although it was not likely that this degree of inhibition could be ascribed to indirect effects upon the stomach by way of the red blood cell and the kidney, another group of experiments was performed to demonstrate that the inhibitors were acting directly on the gastric mucosa. Solutions of 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide in concentration of 2–12 mg./ml. were instilled into these same fundus pouches for 30 or 60 minutes, and the secretory response to histamine retested. Marked inhibition of acid output was again demonstrated. Assay of peripheral venous blood for the inhibitor during some of these experiments indicated that none or only traces were detectable in the circulation. Inhibition of secretion was also induced by direct topical application of 2-benzothiazole-sulfonamide and of Dirnate (an unsubstituted sulfonamide) to the gastric mucous membrane.

These experiments demonstrated clearly that potent carbonic anhydrase inhibitors can inhibit gastric secretion of acid by a direct action on the mucosa in the living animal. This has subsequently been confirmed by others.[10]

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The Role of Carbonic Anhydrase in Acid Secretion. According to current concepts, the hydrogen ions of the gastric juice are derived from water, perhaps by a process of "membrane hydrolysis" at the intracellular canalicular wall.[1] The chloride ions are derived from the blood. Evidence based on the "alkaline tide," the study of arterial-venous differences, and secretion in isolated mucosae indicates that for each mole of chloride ion withdrawn from the blood and secreted into the lumen of the stomach, a mole of bicarbonate is secreted in exchange into the blood.[5, 11] This bicarbonate is derived from (1) blood CO_2 and (2) metabolic CO_2 produced within the parietal cell, both being hydrated to form carbonic acid with the aid of the enzyme carbonic anhydrase. The carbonic acid thus formed serves the dual function of providing bicarbonate ions that are exchanged for chloride ions and, also, of neutralizing the hydroxyl ions (alkali) that accumulate within the cell in consequence of the splitting of water.

The present experiments indicate that the rate of the reaction:

$$H_2O + CO_2 \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

is not rapid enough in the absence of carbonic anhydrase to meet the full demands of an actively secreting gastric mucosa. Consequently, the rate of acid formation falls drastically, but not completely, when the inhibitors are given. This analysis accounts for the shorter latent period for inhibition at higher rates of secretion, when the need for bicarbonate ion is correspondingly increased. The failure to inhibit acid secretion completely is probably the result of (1) the appreciable uncatalyzed rate of formation of carbonic acid; (2) the presence of other buffer anions, such as lactate (recently suggested by Davenport[12]), or possibly even phosphate.

Secretion of Other Ions. Study of the effect of carbonic anhydrase inhibition on the other ions of gastric juice, has revealed no specific effect on Na^+ and K^+.[13] Only HCl formation is inhibited.

Carbonic Anhydrase and the Alkaline Component. Carbonic anhydrase is also present in the surface epithelial cells and in some pyloric cells.[5] These cells are believed to contribute to the alkaline component, but the role of the enzyme here is completely unknown and requires study.

Summary and Conclusions. Potent inhibitors of the enzyme carbonic anhydrase can profoundly inhibit the secretion of hydrochloric acid in living animals. This inhibition can be induced by the direct action of the inhibitors on the gastric mucous membrane.

The present evidence is in keeping with the hypothesis that carbonic anhydrase activity during acid secretion catalyzes the rate at which carbon dioxide is hydrated to form carbonic acid. This serves to neutralize alkali within the parietal cell, and furnishes bicarbonate ions for exchange with the chloride ions of the blood. In the absence of enzyme activity, the rate of this reaction is inadequate for the requirements of an actively secreting gastric mucosa and, consequently, the rate of formation of HCl falls.

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THE ROLE OF CARBONIC ANHYDRASE IN PANCREATIC SECRETION*

By FRANKLIN HOLLANDER AND DAVID BIRNBAUM†

The Basic Hypothesis

The objective of this paper is to organize present knowledge regarding the cellular mechanism of bicarbonate secretion by the pancreas, and to demonstrate the function of carbonic anhydrase in this process. In any attempt to comprehend the microphysiology of this exocrine secretion, the investigator finds himself confronted with a mixture of organic and inorganic substances in widely varying proportions, and of obviously different origins. Hence, in order that the bicarbonate of this mixture be placed in its proper perspective, we propose to view pancreatic juice as a mixture of four distinct components: (1) *Mucus secretion*, comprising one or more glycoproteins derived from typical mucous epithelial cells in the walls of the major pancreatic ducts; (2) *enzyme secretion*, containing all the pancreatic enzymes or zymogens, and arising from the acinar cells of the gland; (3) *a chloride-containing fluid*, possessing a chemical anatomy essentially the same as the electrolyte pattern of interstitial fluid, and possibly identical with it; and (4) *a specific bicarbonate secretion*, containing all the cations of interstitial fluid at similar concentrations,‡ but no chloride or other anion, the total concentration being about 165 mN (*i.e.*, isosmotic with blood plasma).

Concerning the cellular origin of the bicarbonate secretion, two possibilities are evident: (a) the acinar cells, and (b) the flat centro-acinar and terminal-duct cells, which are probably identical. The latter is the more probable source, for the following reasons: Although the acinar cells may play a dual role, this is unlikely because active secretion of either enzymes or HCO_3^- can be induced unaccompanied by major quantities of each other, using pancreozymin or secretin as stimulus under suitable conditions. Similar dissociations occur in pancreatitis and carcinoma of the pancreas in man.[1, 2] Also, the cessation of HCO_3^- (but not enzyme) output in dogs with alloxan diabetes is accompanied by vacuolization only of the duct cells.[3] Consequently, we shall assume these flat cells to be the source of the bicarbonate component.

The Chemical Origin of the Bicarbonate Secretion

What is the source of the CO_2 from which the gland generates $NaHCO_3$ and $KHCO_3$ at about 165 mN? A priori, there are three possibilities: (a) blood HCO_3^-; (b) blood CO_2, converted to HCO_3^- within the cell; and (c) CO_2 generated intracellularly by oxidative metabolism.

In 1928, Woiner[4] reported that continuous pancreatic secretion is accompanied by a decrease in alkali reserve, due to exocrine loss of fixed base. From this he inferred that the HCO_3^- derives as such from blood. Hammarsten and Jorpes,[5] however, and later Oldfedt,[6] found no such decrease. Furthermore, Hammarsten and Jorpes reported that aqueous extracts of pancreatic tissue had an acid reaction (pH 6.74) even in the "resting" state, and an even lower pH value (6.41) when stimulated with secretin. Hence, they concluded that the HCO_3^- is generated by intracellular oxidation, and that all CO_2 in excess of that required for secretion accumulates in the gland. This disagreement was resolved by Still, Bennett, and Scott[7] who studied arterio-venous differences in the pancreatic circulation rather than in systemic blood. During the first few minutes following secretin injection, the concentration of venous CO_2 (free and combined) decreased, sometimes to less than the arterial level but, immediately thereafter, this drop was reversed and venous CO_2 rose above its resting level. In spite of a considerable increase in oxygen consumption during active secretion, in agreement with previous observations,[8, 9] there was an oxygen debt persisting for as long as 30 minutes after cessation of secretion. That oxygen is essential for secretion is further evidenced by the marked suppression of water and HCO_3^- output accompanying anoxia.[10, 11]

It may be concluded from these findings that the gland can use blood CO_2 in small degree. Chiefly, however, it forms its own supply by oxidation, and any HCO_3^- not required for secretion is excreted into the interstitial fluid. Tucker and Ball[13] maintained that at least part of the HCO_3^- derives as such from the blood, and Ball *et al.*[14] estimated that the proportion so derived is at most 20 per cent, with the remainder arising by intracellular metabolism. This dual source of the HCO_3^- is confirmed by other evidence,[12, 13] but the relative importance

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‡ Except that for calcium and magnesium, this similarity relates to the concentrations of the cations not bound by protein.

of these two sources and whether the blood delivers CO_2 or HCO_3^- continues to be in doubt.

The Role of Carbonic Anhydrase

In 1937, Van Goor[15] reported the presence of carbonic anhydrase (CA) in the pancreas of both warm- and cold-blooded animals, from which he postulated that the enzyme catalyzed the conversion CO_2 to H_2CO_3 and therefore HCO_3^- within the gland.[16] Efforts by Tucker and Ball[13] to confirm this presumption by intravenous injection of a CA inhibitor, sulfanilamide, into actively secreting dogs failed to support this, however. Consequently, they asserted that CA is not essential for HCO_3^- formation, and Davenport[17] suggested that "the uncatalyzed reaction may be fast enough to supply all the HCO_3^- necessary."

This failure to inhibit pancreatic secretion with a known inhibitor of CA *in vitro* paralleled the experience with gastric secretion.[19] In 1950, however, Roblin *et al.*[18] synthesized a new CA inhibitor, 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide (Diamox, No. 6063), which proved to be about 400 times as potent as sulfanilamide. Because of its high potency, this compound proved to be effective in our laboratory[20] in blocking gastric HCl formation by histamine by as much as 97 per cent, and this discovery prompted us to study its effect on pancreatic secretion as well.

Our investigation[21] employed unanesthetized dogs provided with a duodenostomy for the purpose of collecting pancreatic juice through a cannula inserted temporarily into the major pancreatic duct outlet.[22, 23]. Intravenously injected secretin was the stimulus. Diamox was also administered intravenously. Significant decreases in secretory response occurred at doses of 10 mg./kg. or greater, the degree of inhibition increasing with dosage. The highest degrees of inhibition were 95 per cent of secretory volume and 97 per cent of HCO_3^- output (meq.). These experiments demonstrate that pancreatic secretion can be inhibited *in vivo* by a CA inhibitor of adequate potency, and therefore that the enzyme probably plays a primary role in formation of the HCO_3^-.

Most (and possibly all) of this ion derives from CO_2 according to the equation:

$$CO_2 + H_2O \xrightarrow[\text{anhydrase}]{\text{Carbonic}} H_2CO_3 \longrightarrow H^+ + HCO_3^-$$

Failure to attain complete inhibition of secretory output may have resulted merely from inadequate dosage of the inhibitor (maximum 60 mg. kg.), but it may also mean that a small part of the HCO_3 is formed without the aid of the catalyst, and that a very small amount may be derived from the blood as the preformed ion. The present investigation affords strong evidence that plasma is not a significant source of this preformed bicarbonate, but it throws no further light on the relative amounts of CO_2 derived from plasma and intraglandular oxidative processes.

Summary

A hypothesis is presented concerning the variable chemical composition of pure pancreatic secretion. It postulates a mixture of four distinct secretions in varying proportions, each having a different cellular source. In particular, evidence is cited to support the premise that the bicarbonate secretion originates in the flat duct- and centroacinar cells. A review of all the available evidence concerning the chemical origin of the bicarbonate ion in this secretion indicates that it is formed from CO_2 which is made available (1) by diffusion from the blood and (2) by oxidative metabolism within the secretory cells. The latter may supply at least 80 per cent of the total. Recent evidence is cited to support the premise that carbonic anhydrase plays a major role in the intracellular conversion of CO_2 to H_2CO_3 and, therefore, in the formation of HCO_3^- for secretion. Following intravenous injection in dogs of a sufficiently potent inhibitor of carbonic anhydrase (Diamox, No. 6063), the bicarbonate output in pancreatic juice stimulated by secretin was reduced as much as 97 per cent.

The small residue of about 3 per cent may represent HCO_3^- either formed from CO_2 without the aid of the enzyme or derived as such from the blood.

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*SECTION OF PHYSICS AND CHEMISTRY**

STUDIES ON THE STRUCTURE OF THE PYRIMIDINE GLUCOSIDE VICINE†

By AARON BENDICH‡

Vicine, a pyrimidine glucoside discovered in 1870[1] and occurring widely in legumes and beet juice,[2] has been assigned the structure shown in FIGURE 1 by Levine,[3] *i.e.*, a 3-*N*-glucoside of divicine, which, according to Levene, is 2,5-diamine-4,6-dioxypyrimidine. Although this conclusion has been generally accepted for 36 years, data have now been

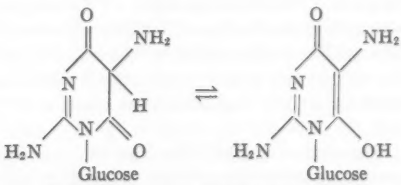

FIGURE 1. P. A. Levene's formulation of vicine.

obtained that are incompatible with this formulation.

An examination of the ultraviolet-absorption spectra of the aglycone, divicine (λ max = 280 mμ in *N*/4 HCl; maxima at 240 and 280 mμ in water), revealed that it was considerably different from that of authentic, synthetic 2,5-diamino-4,6-dioxypyrimidine,[4] which showed λ max = 253 mμ in *N*/4 HCl and 255 in water.

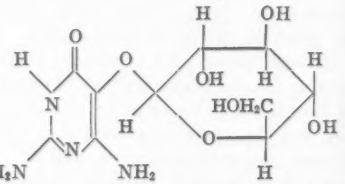

FIGURE 2. Vicine, 2,4-diamino-6-oxypyrimidine-5-(β-D-glucopyranoside).

It is now proposed that vicine be assigned the structure shown in FIGURE 2, namely, 2,4-diamino-6-oxypyrimidine-5-(β-D-glucopyranoside). This conclusion rests upon the following:

(a) The empirical formula, $C_{10}H_{16}O_7N_4$;

(b) The isolation from vicine of D-glucose by Fischer,[5] and by Hérrisey and Cheymol[6] who, in addition, found that vicine is split by emulsin;

(c) Half of the N of vicine as well as of divicine is present as free amino groups (revealed by nitrous acid treatment) one of which is at position 2 (due to the liberation of guanidine following oxidation with chloric acid[3]);

(d) The fact that divicine gives a blue ferric chloric phenolic hydroxyl test whereas vicine does not, indicating that the glucosidic union masks the phenolic hydroxyl, which can only be at position 5;

(e) The strikingly similar ultraviolet-absorption

* The Section of Mathematics and Engineering held a meeting on November 21 at which a paper entitled "Sinusoidal Oscillations in Nonlinear Systems" was read by John B. Russell. The Section of Anthropology held a meeting on November 24 at which a paper entitled "A Quantitative Approach to Indian Social Structure—Caste and Tribe" was delivered by D. N. Majumdar. No abstracts of these papers have been received.

† This paper, illustrated with lantern slides, was delivered at the meeting of the Section on November 11, 1952. This investigation was supported by grants from the National Cancer Institute, National Institutes of Health, United States Public Health Service, and from the Atomic Energy Commission, contract no AT(30-1)-910. The interest and support of Drs. George Bosworth Brown and George H. Hitchings are gratefully acknowledged.

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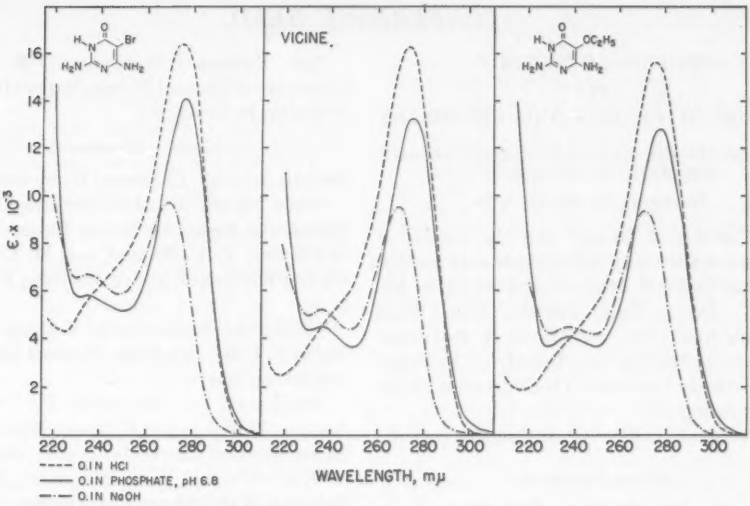

FIGURE 3. Comparison of ultraviolet-absorption spectra of vicine and 2,4-diamino-5-bromo-6-oxypyrimidine and 2,4-diamino-5-ethoxy-6-oxypyrimidine.

spectra of vicine and 2,4-diamino-5-bromo-6-oxypyrimidine and 2,4-diamino-5-ethoxy-6-oxypyrimidine (FIGURE 3);

(f) The consumption by vicine of about two moles of periodate, with the production of no formaldehyde, but rather of about one mole of acid (presumably formic acid).

Additional evidence for the attachment of the glucose moiety at position 5 of the pyrimidine is provided by the fact that neither phosphomolybdate[7] nor dichlorophenolindophenol are reduced by vicine in neutral or alkaline solution, whereas divicine is strongly reducing and shows many of the chemical properties of ascorbic and scorbamic acids.[8] A study of this difference between the aglycone and its glucoside has been made. It appears that enediols (or aminoenols) conjugated to carbonyl (as in ascorbic acid, for example), such as are present in divicine and analogous pyrimidines, require a free hydroxyl (or amino) group at position 5 in order that their striking reducing ability be manifest.[9]

Further details, including studies on the synthesis of divicine, will be published presently.

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CONFERENCE HELD

SECTION OF BIOLOGY
and
SECTION OF PHYSICS AND CHEMISTRY

"ION EXCHANGE RESINS IN MEDICINE AND BIOLOGICAL RESEARCH"

NOVEMBER 14 AND 15, 1952

The Section of Biology and the Section of Physics and Chemistry held a Conference on "Ion Exchange Resins in Medicine and Biological Research." Doctor Harry Sobotka, Mount Sinai Hospital, New York, and Doctor H. P. Gregor, Polytechnic Institue of Brooklyn, Brooklyn, N. Y., were the Conference Co-Chairmen in charge of the meeting.

The program consisted of the following papers:

Friday, November 14

Morning Session. Chairman: H. F. Mark

"Synthesis of Ion Exchange Resins," P. N. Craig, Smith, Kline and French Laboratories, Philadelphia, Pa.

"Electron Exchange Polymers," M. Ezrin and H. G. Cassidy, Sterling Chemical Laboratory, Yale University, New Haven, Conn.

"Thermodynamic Properties," H. P. Gregor, Polytechnic Institute of Brooklyn, Brooklyn, N. Y.

"Equilibrium Constants of Exchange Processes," A. W. Davidson, University of Kansas, Lawrence, Kansas.

Afternoon Session. Chairman: H. P. Gregor

"Kinetics of Exchange Reaction," B. A. Soldano, Oak Ridge National Laboratory, Oak Ridge, Tenn.

"Cation Exchange Processes," J. I. Bregman, National Aluminate Corporation, Park Forest, Ill.

"Polyvalent Cation Exchange," C. Calmon, The Permutit Company, Birmingham, N. J.

"Anion Exchange Process," S. Peterson, Oak Ridge National Laboratory, Oak Ridge, Tenn.

Evening Session. Chairman: T. Shedlovsky

"Ion Exchange Processes," R. M. Wheaton, The Dow Chemical Company, Midland, Michigan.

"Ion Exchange Membranes," K. Sollner, Laboratory of Physical Biology, National Institutes of Health, Bethesda, Md.

Saturday, November 15

Morning Session. Chairman: Harry Sobotka

"Some Aspects of Cation Exchange Resins as Therapeutic Agents for Sodium Removal," E. W. McChesney, F. C. Nachod, and M. L. Tainter, Sterling-Winthrop Research Institute, Rensselaer, N. Y.

"Biochemical Separations by Exchange Resins," Waldo E. Cohn, Oak Ridge National Laboratory, Oak Ridge, Tenn.

"Purification of Antibodies by Means of Antigens Linked to Ion Exchange Resins," H. C. Isliker, Harvard University, Boston, Mass.

"Electrolyte and Water Movement Across the Intestinal Wall," Maurice D. Visscher, University of Minnesota, Minneapolis, Minn.

"Exchange Resins as Diagnostic Tool," Harry L. Segal, University of Rochester, Rochester, N. Y.

Afternoon Session. Chairman: William Dock

"Considerations in the Selection of Cation Exchange Resins for Therapeutic Use," A. E. Heming, Smith, Kline and French Laboratories, Philadelphia, Pa.

"The Role of the Gastro-Intestinal Tract in the Adaption of the Body to Prolonged Sodium Depletion Induced by Cation Exchange Resins," Kendall Emerson, Jr., Peter Bent Brigham Hospital, Boston, Mass.

"Clinical Experience with Mixtures of Anion and Cation Exchange Resins," K. C. Kohlstaedt, B. L. Martz, R. S. Griffith, and O. M. Helmer, Lilly Laboratory for Clinical Research, Indianapolis, Ind.

"Biochemical and Clinical Observations during Cation Exchange Resin Therapy," T. S. Danowski, University of Pittsburgh, Pittsburgh, Pa.

"Interpretation of Laboratory Data in Exchange Resin Therapy," M. Levitt, Mount Sinai Hospital, New York, N. Y.

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